CHPA
FOUNDED 1881

Producers of Quality Nonprescription Medicines and Dietary Supplements for Self-Care

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION®

February 1, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 01N-0397

SUBJECT: Second Follow-up Submission by CHPA to the FDA/NTSB Joint Public Meeting on Transportation Safety and Potentially Sedating or Impairing Medications: Comments on the Safety of OTC Antihistamines and OTC Labeling

To Whom It May Concern:

On December 17, 2001, the Consumer Healthcare Products Association (CHPA)[1] submitted detailed comments supporting its position that:

- A thorough review of FDA's AER system and other information indicates that there are no unexpected signals for concern relating to accidents associated with OTC antihistamines;
- Neither the available data from FDA's adverse experience reporting system nor the unproven nature of pictograms in an OTC setting provides any support for changes in OTC labels to bring further prominence to drowsiness warnings on OTC antihistamines, either by pictograms, symbols or other means.

At the time of the submission of CHPA's December 17th comments, the transcript of the November 14-15 meeting was not available. Since a number of expert

[1] CHPA is a 120-year-old trade organization representing the manufacturers and distributors of nonprescription (or over-the-counter, OTC) medicines and dietary supplements. CHPA represents over 95% of the nonprescription medicines market by sales. CHPA members market all the major national brand and store brand antihistamine-containing nonprescription products in the United States.

1150 Connecticut Avenue, N.W. • Washington, D.C. 20036-4193 • Tel: 202-429-9260 • Fax: 202-223-6835 • www.chpa-info.org

witnesses invited by the government were supportive of the perspective and conclusions provided in CHPA's December 17th submission, CHPA stated that it would be submitting an addendum to its comments, highlighting certain important aspects of statements of the expert witnesses that are supportive of the association's position.

In addition, one witness commented that the antihistamines included for study by Ray et al.[2] were second generation antihistamines[3]. At the joint hearing of FDA and NTSB (National Transportation Safety Board) on November 14-15, 2001, CHPA presented the study by Ray et al. as supportive of the safety of first generation over-the-counter (OTC) antihistamines. We have clarified this apparent discrepancy in support of our position.

We ask that FDA accept this addendum to CHPA's December 17th comments as information important to the consideration of the safety of OTC antihistamines. These comments are organized in two parts, the first addressing a summary of the study by Ray et al., and the second highlighting several aspects of the meeting, as expressed in the transcript.

I. Ray, W.A. et al: Psychoactive Drugs and the Risk of Injurious Motor Vehicle Crashes in Elderly Drivers. *Am. J. Epidemiol.* 136(7): 873-83, 1992.

During Q&A on the epidemiology panel of the November 14-15 FDA/NTSB meeting, one invited participant maintained that the antihistamines studied in the Tennessee database analyzed by Ray et al. did not contain "sedating antihistamines" (i.e., first generation antihistamines; see transcript of November 14th at page 218; web-based copy). Subsequent to the meeting, CHPA followed up with the Tennessee Department of Health, and received a report that the antihistamines assessed in the Medicaid files by Ray et al. were in fact prescription versions of first generation antihistamines. Based on

[2] Ray, W.A. et al: Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers. Am. J. Epidemiol. 136(7): 873-83, 1992.

[3] Second generation are currently are available only with a doctor's prescription. By contrast, first generation antihistamines include the following, which are available over-the-counter: brompheniramine; dexbrompheniramine; chlorpheniramine; cyclizine; dexchlorpheniramine; dimenhydrinate; diphenhydramine; doxylamine; meclizine; phenindamine; pyrilamine; triprolidine.

this follow-up report, we submit herein the study by Ray et al. as further support for the position that there are no unexpected signals for concern, in either FDA's AER database or in other information including the published literature, relating to accidents associated with OTC antihistamines.

Specifically, the study by Ray et al. determined the risks for an injurious crash for drivers who had received prescriptions for various drugs, using prescription and crash records for 16,262 elderly (65-84) drivers in Tennessee. The relative risks found for current users of the following drugs were, for example: 1.5 for any psychoactive prescription drug (95 percent CI 1.1-2.0); 2.2 for cyclic antidepressants (95 percent CI 1.3-3.5); 1.5 for benzodiazepines (95 percent CI 1.1-2.0); and 2.1 for users of both benzodiazepines and antidepressants (95 percent CI 1.1-4.2). However, the relative risk for current users of only Rx first generation antihistamines was 1.2 (95 percent CI 0.6-2.4), and no dose effect demonstrable. These findings indicate that the overall relative risk of injurious crash involvement for current elderly users of benzodiazepines, cyclic antidepressants, Rx antihistamines, and opiod analgesics is confined to the first two classes of drugs. It should be noted that this study did not assess OTC use of first generation antihistamines, having derived prescription drug use by the elderly from Medicaid files. (Medicaid files would not be expected to include data for OTC products because they are typically not covered by this medical coverage). Nevertheless, the study indicates a very low reported involvement of prescription first generation antihistamines in crashes during the period studied, and the CHPA AER analysis[4] covering much of the period following this study is consistent with this view.

The study by Ray et al. should therefore be included with the studies by the National Highway Traffic Safety Administration (NHTSA)[5], the study by Turnbridge et

[4] Submitted in CHPA's December 17th Comments to the Docket.

[5] Terhune, K. W. et al.: The incidence and role of drugs in fatally injured drivers. U.S. Department of Transportation, National Highway Traffic Safety Administration Report No.: DOT HS 808 065, October 30, 1992.

al.[6], and the study by Leveille et al.[7] as support for the conclusion that first generation antihistamines have little effect of risk of traffic accidents, as concluded for example by Leveille et al. (see CHPA December 17th submission).

II. Highlights of the Transcript of the November 14-15 FDA/NTSB Meeting

Two aspects of the transcript of the November 14-15 meeting should be highlighted because they reiterate and underscore arguments presented by CHPA: one pertaining to epidemiology; the other to labeling.

First, with respect to the epidemiology, Dr. Mitchell Garber (Medical Officer) of the NTSB asked the epidemiology panelists to comment on the CHPA presentation in the context of the question: "Do you agree with that assessment, that the sedating antihistamines are likely not a problem, based on adverse event experience reporting?" (See transcript at page 191-192; web-based copy.) In response, the panelists replied:

> MR. WAYNE JEFFERY (Toxicology Services, RCMP Forensic Laboratory, Vancouver, BC): In the BC data, we only had one fatal motor vehicle accident caused by the antihistamines, and yes, I'd agree with them. I mean, on the scale of impairing drugs, it's at the lower level. There are other drugs that we're more interested in, yes.
>
> DR. GARBER (NTSB): Any of the other --
>
> DR. FIONA COUPER (Washington State Toxicological Laboratory, Washington State Patrol, Seattle, WA): I would essentially agree with that. The cases, though, that we've seen with the sedating antihistamines, diphenhydramine for example, the people are taking them in huge amounts. They're not therapeutic doses at all. Just the toxicology, the blood results in and of themselves must mean that they're taking way above the therapeutic levels.
>
> So, in that regard, yes, they are probably very sedating, but normal therapeutic doses, no, we're not seeing those in our cases.
>
> MS. JUDY STEVENS (National Center for Injury Prevention and Control, Centers for Disease Control, Atlanta, GA): Most of the epidemiologic

[6] Turnbridge, R., Clark, A., Ward, N., Dye, L., and Berghaus, G.: Prioritizing drugs and medicines for development of roadside impairment testing. CERTIFIED-DR1, University of Leeds (Work funded by the European Commission), 2000.

[7] Leveille, S. G. et al.: Psychoactive medications and injurious motor vehicle collisions involving older drivers. Epidemiology 5: 591-598, 1994.

> studies that have tried to look at these were looking at only the prescribed antihistamines, and there is really no way of knowing whether people were taking over-the-counter medications from the records. So, that really is something that needs to be looked at, I think, a little bit further.
>
> MR. DOUGLAS ALLEN(Alcohol and Drug Program Management, Federal Rail Administration, Washington, DC): I would have to say the same thing because we're, as you just pointed out, looking for the prescribed medications as opposed to the over-the-counter, and the data reflects that we have not found it in our reviews.

Hence, there was no evidence presented to challenge the CHPA presentation that included both published epidemiologic studies and a detailed review of the adverse experience reports (AERs) pertaining to OTC first generation antihistamines over the past ten years.

Second, with respect to labeling. No evidence was presented to provide empirical support for the use of pictograms or icons on the OTC label. Furthermore, in relation to the use of the red triangle in Norway and a yellow triangle in Denmark, Dr. de Gier (Ultrecht Institute for Pharmaceutical Science, The Netherlands) provided a rather disconcerting view that such icons are widely misinterpreted and/or ignored, as follows (see transcript at pages 442 and 449; web-based copy):

> DR. JOHANN de GIER (Ultrecht Institute for Pharmaceutical Science, The Netherlands): In Norway, and probably you will explain a little bit more, the Red Triangle system was introduced in 1981 and later on in 1983 in all the Nordic countries. And -- but also here, hard to say how effective it was. In 1987 there was an evaluation in Sweden that actually explained that three years after the implementation that 50 percent of the patients receiving a medication with a red triangle on the medication box did not really understand the meaning of it. They thought it was something that indicated poison or that it was to keep it out of reach of children. So, there was not an understanding that all the patients understood what was going on.
>
> And also in the Netherlands we looked at that and we found out that one-third of the patients receiving that yellow sticker actually took any action, which means not drive at all, drive less, or in some situations also stopped taking the medication, which of course is not the right thing to do if you are treating some kind of a disease.
>
> ...
>
> DR. de GIER: Well, with respect to the responsibilities in transportation safety and public health, I think that even the existing systems but also if we would like to follow the Nordic countries by introducing the red triangle, we still

need to have a good evaluation before and after implementation of the effect of this kind of warning system and we're still lacking that.

Hence, based on a review of the transcript of the November 14-15 FDA/NTSB meeting, CHPA concludes that no additional information was presented that would challenge the conclusions made by the association at the meeting and in its follow-up comments pertaining to epidemiologic and labeling issues.

III. Conclusion

In conclusion, CHPA maintains that OTC antihistamines are generally recognized as safe and effective and properly labeled. Information presented by the association at the November 14-15 FDA/NTSB meeting and in previous follow-up comments supports this conclusion. This second follow-up submission highlights aspects of the transcript and clarifies the epidemiologic database used by Ray et al., all of which continues to support the association's position on the safety of first generation antihistamines.

Respectfully submitted by:

R. William Soller, Ph.D.
Senior Vice President and
Director of Science & Technology

Attachment: Correspondence between CHPA and Dr. Wayne Ray, including Dr. Rays' published study: Ray, W.A. et al: Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers. *Am. J. Epidemiol.* 136(7): 873-83, 1992.

WS/jq:OTC Ingredients/Antihistamines/Post Transcript Submission Ahs FDA NTSB 1

Quaempts, Judith
From: Bradley, Bill
Sent: Friday, February 01, 2002 2:12 PM
To: Soller, Bill; Quaempts, Judith
Subject: FW:

-----Original Message-----
From: **Bradley, Bill**
Sent: Wednesday, January 02, 2002 7:59 AM
To: 'Cindy.Naron@mcmail.vanderbilt.edu'
Subject: RE:

Thank you very much.

Bill Bradley

-----Original Message-----
From: **Cindy.Naron@mcmail.vanderbilt.edu [mailto:Cindy.Naron@mcmail.vanderbilt.edu]**
Sent: Friday, December 28, 2001 4:11 PM
To: Bradley, Bill
Subject:

Dear Dr. Bradley:

Dr. Ray received a fax from you on December 10, 2001, regarding one of his published studies in the 1992 American Journal of Epidemiology.

Dr. Ray has asked that I respond with the following:

Dear Dr. Bradley:

Thank you for your recent inquiry regarding out previous study. As you surmised, only the first-generation anti-histamines were included in our study.

Best Regards.

Wayne A. Ray, Ph.D.
Professor and Director
Division of Pharmacoepidemiology

CHPA
FOUNDED 1881

Consumer Healthcare Products Association

FAX TRANSMISSION

Consumer Healthcare Products Association
1150 Connecticut Ave., N.W.
Washington, DC 20036
Phone 202-429-9260 Fax 202-223-6835
www.chpa-info.org

Date: December 10, 2001

To: Dr. Wayne A. Ray

Number of pages (including this cover page) 1

Dr. Ray,

In 1992, you published a study in the American Journal of Epidemiology called "Psychoactive Drugs and the Risk of Injurious Motor Vehicle Crashes in Elderly Drivers."

One of the classes of drugs studied was antihistamines. It was unclear from the paper whether these included only second-generation (non-sedating) antihistamines, or also the first-generation (sedating) antihistamines. In the 1984-1988 time period of the study, the only non-sedating antihistamine would have been terfenidine (Seldane). The major Rx sedating antihistamine would have been diphenhydramine (Benedryl) with some prescriptions for chlorpheniramine.

Was there a distinction made between the two classes of antihistamines, or is there any way of determining whether both classes were included in the study analysis.

I would greatly appreciate your help on this important question, and eagerly await your reply.

Thank you in advance.

William W. Bradley
Vice President - Technical Affairs
Consumer Healthcare Products Association
Phone 202-429-9260
Fax 202-223-6835
bbradley@chpa-info.org

American Journal of Epidemiology
Vol. 136, No. 7

Printed in U.S.A.

Psychoactive Drugs and the Risk of Injurious Motor Vehicle Crashes in Elderly Drivers

Wayne A. Ray, Randy L. Fought, and Michael D. Decker

To determine whether commonly used psychoactive drugs increase the risk of involvement in motor vehicle crashes for drivers ≥65 years of age, the authors conducted a retrospective cohort study. Data were obtained from computerized files from the Tennessee Medicaid program, driver's license files, and police reports of injurious crashes. Cohort members were Medicaid enrollees 65–84 years of age who had a valid driver's license during the study period 1984–1988 and who met other criteria designed to exclude persons unlikely to be drivers and to ensure availability of necessary study data. There were 16,262 persons in the study cohort with 38,701 person-years of follow-up and involvement in 495 injurious crashes. For four groups of psychoactive drugs (benzodiazepines, cyclic antidepressants, oral opioid analgesics, and antihistamines), the risk of crash involvement was calculated with Poisson regression models that controlled for demographic characteristics and use of medical care as an indicator of health status. The relative risk of injurious crash involvement for current users of any psychoactive drug was 1.5 (95% confidence interval (CI) 1.2–1.9). This increased risk was confined to benzodiazepines (relative risk = 1.5; 95% CI 1.2–1.9) and cyclic antidepressants (relative risk = 2.2; 95% CI 1.3–3.5). For these drugs, the relative risk increased with dose and was substantial for high doses: 2.4 (95% CI 1.3–4.4) for ≥20 mg of diazepam and 5.5 (95% CI 2.6–11.6) for ≥125 mg of amitriptyline. Analysis of data for the crash-involved drivers suggested that these findings were not due to confounding by alcohol use or driving frequency. *Am J Epidemiol* 1992;136:873–83.

accidents, traffic; analgesics, addictive; antidepressive agents; benzodiazepines; histamine H_1 receptor blockaders; psychotropic drugs

For older persons in the United States today, continuing to drive is frequently essential to maintaining independence. In 1986, 58 percent of persons 65 years of age or older held driver's licenses, and many continue to drive into the ninth decade of life (1). However, the ability of the older driver to safely operate a motor vehicle may be adversely affected by the decreases in sensory, cognitive, and motor function and the increase in prevalence of illness that accompany aging (2, 3). For drivers 65 years of age or older, the rate of involvement in motor vehicle crashes per mile driven increases exponentially with age (4). Thus, there has been considerable recent interest (3–7) in elucidating the factors that influence the safety of older drivers. These data are essential to development of policies regulating testing and relicensing of the older driver, to physician counselling of older patients, and to implementation of preventive measures.

Received for publication October 4, 1991, and in final form March 25, 1992.

Abbreviation: CI, confidence interval.

From the Department of Preventive Medicine, Vanderbilt University School of Medicine, Nashville, TN.

Reprint requests to Dr. Wayne A. Ray, Department of Preventive Medicine, A-1124 MCN, Vanderbilt University School of Medicine, Nashville, TN 37232-2637.

Supported by grants from the Centers for Disease Control (200-85-0874), Atlanta, GA, and the Food and Drug Administration (FD-U-0000073), Rockville, MD.

We gratefully acknowledge the assistance of Susan Patterson in manuscript preparation.

The use of psychoactive drugs may interfere with the older driver's ability to safely operate a motor vehicle (3, 8–10). These medications are known to produce general psychomotor impairment in persons 65 years of age or older (11–16). For persons less than 65 years of age, there is an extensive body of experimental research that shows that benzodiazepines produce a dose-related impairment in performance on tests of driving-related psychomotor skills, including reaction time (17), stimulus detection (18), hand-eye coordination (19), and simulated driving (20–22). O'Hanlon et al. (23) have demonstrated that a single dose of 10 mg of diazepam given to healthy young males impaired road-tracking ability during uninterrupted high-speed highway driving. Similar adverse effects on performance in the laboratory or on the road have been demonstrated for other benzodiazepines (24–26), barbiturates (26), cyclic antidepressants (27), opioid analgesics (10), and sedating antihistamines (28). There are limited epidemiologic data that suggest that psychoactive drugs increase risk of involvement in crashes (29–31), although this finding is still controversial (32).

However, although psychoactive drugs are among the most frequently used medications in elderly populations (33), little is known concerning their effects on driving performance or on risk of motor vehicle crashes for drivers 65 years of age or older. To address this latter question, we performed a retrospective cohort study of the risk of involvement in injurious motor vehicle crashes in a defined population of older licensed drivers.

MATERIALS AND METHODS

Sources of data

Study design. The study subjects were persons 65–84 years of age who were enrolled in Tennessee Medicaid at some time during the study period 1984–1988 who had a valid driver's license and met several other entry criteria designed to exclude persons unlikely to be regular drivers and to ensure that necessary study data were available. The study was conducted among elderly Medicaid enrollees because the Medicaid program kept computerized records of prescriptions filled at the pharmacy, providing a detailed and unbiased indicator of the use of psychoactive drugs. However, because the majority of enrollees under 65 years of age consist of children, young women, and the severely disabled (34), this data source is less suitable for studying the effects of psychoactive drugs in younger drivers. Computerized files maintained by the Tennessee Department of Safety were used to identify Medicaid enrollees with driver's licenses and their involvement in motor vehicle crashes.

Medicaid files. The enrollment file identified persons who were eligible to receive Medicaid benefits. It included each enrollee's Medicaid number, name, address, social security number, date of birth, dates and basis of Medicaid enrollment, sex, race, county of residence, and date of death (34). The pharmacy file contained a record of each prescription for drugs filled for outpatients and reimbursed by Medicaid. Each record identified the patient's Medicaid number, the date the prescription was filled, the drug name and quantity dispensed, and the anticipated duration of the prescription (days of supply). Other files contained information on inpatient hospital admissions, emergency room visits, and nursing home stays. The Medicaid data elements used for this study have a high level of accuracy and completeness (35), because they are required for provider payments and thus are subject to periodic audits.

Driving files. The driver's license file maintained a cumulative record of persons issued a Tennessee driver's license. The file included each person's license number, name, address, social security number, sex, date of birth, type of license, most recent renewal (or issue) date, previous renewal date, and termination (expiration, revocation, suspension, or cancellation) date. This file was linked with the Medicaid enrollment file to identify enrollees who held valid driver's licenses. The Tennessee motor vehicle crash file contained records for crashes reported to the Tennessee Department of Safety. Re-

ports are required by law for crashes that involve injury or property damages of $200 or more. Each record identified the date and time of the crash and the number of involved vehicles. For each of these vehicles, the record further identified the license number of the driver, injury to any occupant or pedestrian, the estimated amount of property damage, an estimate of the speed at which the vehicle was travelling, and whether or not there was evidence of driver use of alcohol (police reports and, for 1987–1988, results of blood alcohol tests). In 1986, the rate of involvement in any reported crash for Tennessee-licensed drivers 65–84 years of age was 38 per 1,000, which was similar to the rate of 40 per 1,000 for all United States-licensed drivers in this age group estimated from the National Accident Sampling System (1).

Study cohort

The cohort inclusion criteria were age 65–84 years, Medicaid enrollment for ≥365 days, and holding a valid driver's license. The exclusion criteria were residence in a nursing home, blindness, medically needy Medicaid enrollment (persons who met all criteria for Medicaid eligibility except income, which, after deduction of allowed medical expenses, fell below the income standard (36)), and treatment consistent with dementia (defined as receipt of more than a single prescription for an antipsychotic drug or a dihydrogenated ergot alkaloid). Although persons qualifying for the study at any time between 1984 and 1988 were included in the cohort, the analysis was confined to that person-time for which all entry criteria were met. Thus, for each person in the cohort, study person-time began on January 1, 1984, or the subsequent first date that all study entry criteria were met. Person-time ended on the earliest of these dates: December 31, 1988, date of first crash in the study, date of death, or first date when any of the study entry criteria ceased to be met. The person-time during and shortly after hospital stays (date of admission through 30 days following discharge) was excluded because records of medications received in the hospital were not present in the Medicaid pharmacy files.

Drug exposure

We studied four classes of psychoactive drugs: benzodiazepines, cyclic antidepressants, oral opioid analgesics, and antihistamines. With the exception of the benzodiazepine hypnotics flurazepam and triazolam, the Medicaid formulary included all drugs in these classes that were commonly used during the study years. We considered other types of drugs with central nervous system effects, including other sedatives, monoamine oxidase inhibitors, lithium, centrally acting skeletal muscle relaxants, injectable opioid analgesics, opioid preparations for treatment of cough or diarrhea, and phenothiazine antiemetics. However, the aggregate rate of use for all of these drugs was only 1.5 percent; therefore, they were not considered in the analysis.

Each person-day of follow-up was classified according to potential use of the study drugs. *Current use* was defined as the period from the day following the dispensation of the prescription through the day following the last scheduled day of supply. Persons in the cohort were thought to be most likely to be exposed to drug effects during this period. *Indeterminate use* consisted of the day the prescription was dispensed and the 60 days following the end of current use. Because this period was likely to include days of both drug use and nonuse, it was analyzed separately to reduce misclassification. *Former use* included the remainder of the 365 days following the end of current use. This period consisted of person-time with a recent history of study drug use, but low likelihood of current use. *Nonuse* encompassed all other person-time.

Current-use person-time was further classified by dose and duration. For each individual drug, the dose was calculated from the most recently filled prescription for that drug by dividing the total quantity of drug received by the days of supply. With the use of standard conversion factors for the drug

class (37), the dose was then converted into equivalent units. To obtain the total dose for a drug class, we summed the doses for all individual drugs in the class. Duration was defined as the number of days of uninterrupted current use.

Injurious crashes

The study outcome was involvement of a cohort member as a driver in a crash reported to the Tennessee Department of Safety in which someone was injured. We did not study crashes that only resulted in property damage because these may be substantially underreported. To check the completeness of injury reporting, we identified those crashes involving a cohort driver who had an emergency room visit, hospitalization, or death within 1 day following the crash. Of these, 86 percent had an injury report in the crash file.

Analysis

Unadjusted rates of crash involvement were calculated by dividing the number of crashes by person-years (person-days/365) of study person-time. Confidence intervals were calculated assuming a Poisson distribution for the number of crashes. The rate of crashes by psychoactive drug use, adjusted for several potential confounders, was estimated from Poisson regression models (38) using the GLIM program (39). The initial model included terms for psychoactive drug use, demographic characteristics, length and basis of Medicaid enrollment, and use of medical care in the previous 365 days. The medical care variables, which provided several indirect measures of health status, consisted of ten terms: one for number of emergency room visits, one for prior hospitalization, and eight for use of nonpsychoactive drugs (antihypertensives, other cardiovascular drugs, hypoglycemic agents, bronchodilators, antiulcer drugs, antimicrobials, nonsteroidal antiinflammatory drugs, and other drugs). This model was simplified through backward elimination to one that included terms for the psychoactive drugs, sex, race, residence in an urban county (defined as a county with a city of 100,000 or larger), age, and calendar year. The estimates of psychoactive drug effects from these two models did not differ materially.

For each category of psychoactive drug use, adjusted rates of crash involvement were calculated by the method of marginal prediction (40), using the regression coefficients from the Poisson model. Relative risk was estimated directly as the antilogarithm of the regression coefficients. The reference exposure category was that of nonuse of any of the study drugs. The test for dose-response trend was performed by calculating for current users the orthogonal linear polynomial contrast of the regression coefficients and its estimated variance (41). Statistical significance was defined as p (two sided) ≤ 0.05.

To assess whether alcohol use was a confounder, we grouped cohort drivers involved in an injurious crash by psychoactive drug use on the date of the crash. We then calculated the proportions of reported alcohol use in each of these groups of drivers. If alcohol were a confounder, then these proportions would differ (34).

We performed a case-crossover analysis (42) to assess whether other unmeasured factors, such as driving practices, were confounders. This analysis, which was restricted to drivers involved in injurious crashes (cases) who had periods of both use and nonuse of psychoactive drugs, is appropriate for episodic exposures where risk is increased only during periods of exposure. It controls for confounding by subject characteristics that do not change during periods of exposure (42). Each case is considered as a separate stratum. Under the null hypothesis, the probability that the case was exposed at the time of the crash depends upon the ratio of total exposed to total unexposed person-time for that case. Thus, a summary (over all strata) Mantel-Haenszel estimator (43) of the rate ratio (and the estimated variance of its logarithm) can be calculated to estimate the relative risk during periods of exposure.

TABLE 1. Unad
Medicaid crash

	Entire
Sex	
Mal	
Fem	
Race	
Wh	
Bla	
Resid	
Urb	
No	
Age	
<7	
≥7	
Year	
19	
19	

* CI, confidenc

RESULTS

There we
cohort, wh
follow-up.
495 injuri
1,000 pers
slightly hig
for all drive
age in Te
dence of cr
nonwhites.
counties.
monly occ
were at sp
hour), inv
caused pr
For cur
the relati
crashes w
percent c
ble 3). In
users was
was not
increased
choactiv
risks of
rent use
cent CI

TABLE 1. Unadjusted rate of involvement in injurious crashes, by demographic characteristics: Tennessee Medicaid crash study, 1984–1988

	Person-years	No. of crashes	Rate per 1,000	95% CI*
Entire cohort	38,701	495	12.8	11.7–13.9
Sex				
Male	21,403	320	15.0	13.3–16.6
Female	17,298	175	10.1	8.6–11.6
Race				
White	29,408	348	11.8	10.6–13.0
Black	9,293	147	15.8	13.2–18.4
Residence				
Urban	8,052	135	16.8	14.0–19.6
Nonurban	30,649	360	11.7	10.5–12.9
Age				
<75 years	24,559	319	13.0	11.6–14.4
≥75 years	14,142	176	12.4	10.6–14.2
Years				
1984–1985	15,139	197	13.0	11.2–14.8
1986–1988	23,562	298	12.6	11.2–14.0

* CI, confidence interval.

RESULTS

There were 16,262 persons in the study cohort, who had 38,701 person-years of follow-up. These persons were involved in 495 injurious crashes, a rate of 12.8 per 1,000 person-years (table 1), which was slightly higher than that of 10.6 per 1,000 for all driver's license holders of comparable age in Tennessee. In the cohort, the incidence of crashes (table 1) was higher in men, nonwhites, and persons living in urban counties. The crashes (table 2) most commonly occurred between 6 a.m. and 7 p.m., were at speeds of less than 45 mph (72 km/hour), involved more than one vehicle, and caused property damage of more than $500.

For current users of psychoactive drugs, the relative risk of involvement in injurious crashes was significantly increased to 1.5 (95 percent confidence interval (CI) 1.2–1.9) (table 3). In contrast, the relative risk for former users was 1.1 (95 percent CI 0.8–1.4), which was not significantly different from 1. The increased risk among current users of psychoactive drugs was due to increased relative risks of 1.5 (95 percent CI 1.1–2.0) for current users of benzodiazepines, 2.2 (95 percent CI 1.3–3.5) for cyclic antidepressants, and 2.1 (95 percent CI 1.1–4.2) for concurrent users of both types of drugs. However, the relative risk for current users of only antihistamines or opioid analgesics was 1.1 (95 percent CI 0.7–1.8). These two classes of drugs were analyzed together because the relative risks for each were similar (relative risk = 1.2 (95 percent CI 0.6–2.4) for current antihistamine use; relative risk = 1.1 (95 percent CI 0.5–2.4) for current opioid analgesic use). There were no dose effects for these drugs and no modification of the effect of other psychoactive drugs.

TABLE 2. Characteristics of injurious crashes: Tennessee Medicaid crash study, 1984–1988

Characteristics	% of crashes
Time of day	
6 a.m.–12 p.m.	38.6
1 p.m.–7 p.m.	53.7
8 p.m.–5 a.m.	7.7
Speed ≥ 45 mph*	37.4
Involved single vehicle	13.7
Property damage > $500	74.9

* Metric conversion: 72 km/hour.

For current users of benzodiazepines or cyclic antidepressants, the risk of involvement in injurious crashes increased with

TABLE 3. Relative risk of involvement in injurious crashes, by use of psychoactive drugs: Tennessee Medicaid crash study, 1984–1988

Psychoactive drug use	Person-years	No. of crashes	Rate* per 1,000	Relative risk	95% CI†
None in 365 days	21,578	254	11.3	1.0	Reference
Former use	6,600	77	12.0	1.1	0.8–1.4
Indeterminate use	4,993	76	16.2	1.4	1.1–1.9
Current use: any psychoactive drug	5,530	88	17.2	1.5	1.2–1.9
Benzodiazepine or cyclic antidepressant	4,215	72	18.8	1.7	1.3–2.2
Benzodiazepine	2,978	46	16.7	1.5	1.1–2.0
Cyclic antidepressant	844	18	24.4	2.2	1.3–3.5
Both benzodiazepine and cyclic antidepressant	393	8	23.9	2.1	1.1–4.2
Antihistamine or opioid analgesic only	1,315	16	12.5	1.1	0.7–1.8

* Rates adjusted for age, sex, race, county of residence, and calendar year with Poisson regression, using the method of marginal prediction.
† CI, confidence interval.

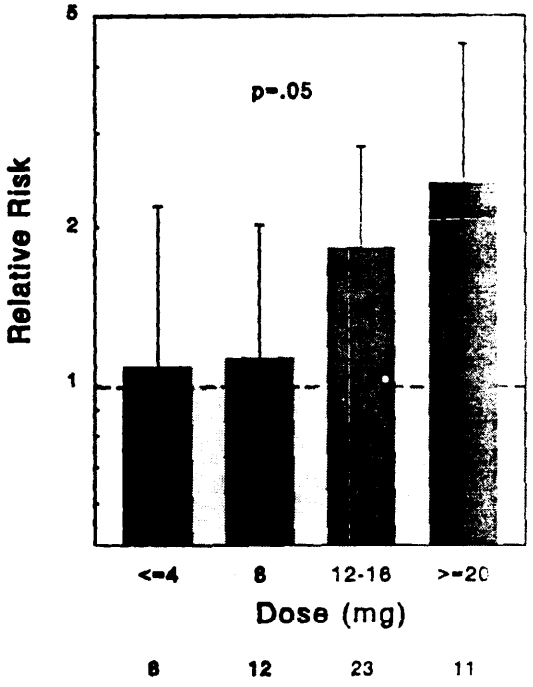

FIGURE 1. Relative risk of involvement in injurious crashes for current users of benzodiazepines, by dose in diazepam equivalents. Numbers below dose, number of cases; vertical bars, upper half of the 95% confidence interval. Tennessee Medicaid Crash Study, 1984–1988.

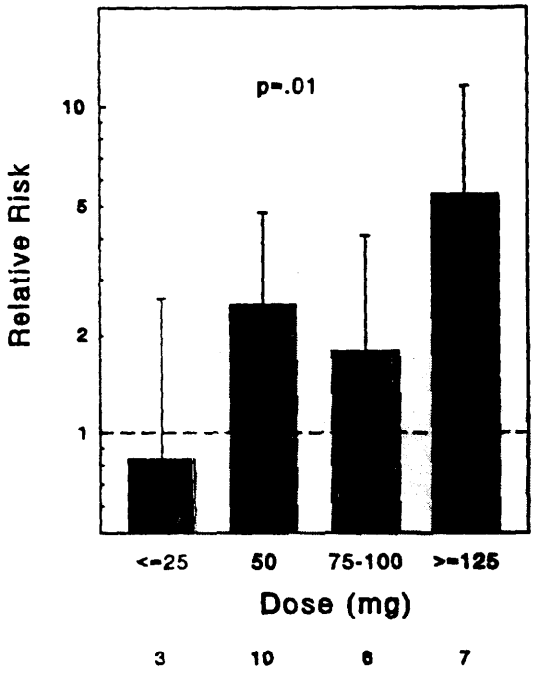

FIGURE 2. Relative risk of involvement in injurious crashes for current users of cyclic antidepressants, by dose in amitriptyline equivalents. Numbers below dose, number of cases; vertical bars, upper half of the 95% confidence interval. Tennessee Medicaid Crash Study, 1984–1988.

increasing dose. For benzodiazepines (figure 1), the relative risk increased from 1.1 (95 percent CI 0.5–2.2) for the equivalent of 4 mg of diazepam or less to 2.4 (95 percent CI 1.3–4.4) for 20 mg or more ($p = 0.05$, test for linear trend). For cyclic antidepressants (figure 2), the relative risk increased from 0.8 (95 percent CI 0.3–2.7) for the equivalent of 25 mg of amitriptyline or less to 5.5 (95 percent CI 2.6–11.6) for 125 mg or more ($p = 0.01$, test for linear trend).

Concurrent
azepines or t
sants was ass
crease in risk
crash (figure
relative risk i
CI 1.1–2.0) f
zodiazepine t
for use of m
cyclic antidc
from 2.0 (95
use of a sing
2.4–39.5) fo
0.03).
The risk of
significantly
pine or cycli
zodiazepines
≤ 30 days fo
90 days for
for 78 perce
were 1.3 (9
percent CI (

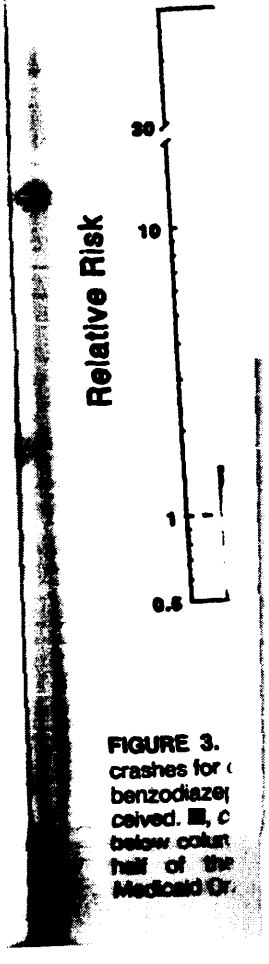

FIGURE 3.
crashes for
benzodiaze
ceived. ■, c
below colun
half of the
Medicaid Cr

Concurrent use of two different benzodiazepines or two different cyclic antidepressants was associated with a pronounced increase in risk of involvement in an injurious crash (figure 3). For benzodiazepines, the relative risk increased from 1.5 (95 percent CI 1.1–2.0) for current use of a single benzodiazepine to 4.8 (95 percent CI 1.6–14.5) for use of more than one ($p = 0.05$). For cyclic antidepressants, the risk increased from 2.0 (95 percent CI 1.3–3.1) for current use of a single drug to 9.8 (95 percent CI 2.4–39.5) for use of more than one ($p = 0.03$).

The risk of crash involvement did not vary significantly with duration of benzodiazepine or cyclic antidepressant use. For benzodiazepines, the duration of drug use was ≤ 30 days for 13 percent of current use, 31–90 days for 9 percent of use, and > 90 days for 78 percent; the respective relative risks were 1.3 (95 percent CI 0.6–2.9), 1.6 (95 percent CI 0.7–3.8), and 1.6 (95 percent CI 1.1–2.2). For cyclic antidepressants, the duration of drug use was ≤ 30 days for 16 percent of current use, 31–90 days for 10 percent of use, and > 90 days for 74 percent; the respective relative risks were 1.6 (95 percent CI 0.5–4.8), 2.5 (95 percent CI 0.8–7.6), and 2.2 (95 percent CI 1.4–3.5). There were no statistically significant differences in risk of crash involvement between the individual drugs. Diazepam accounted for 38 percent of current benzodiazepine use, lorazepam for 29 percent, chlordiazepoxide for 16 percent, clorazepate for 9 percent, and other drugs for 8 percent. Amitriptyline accounted for 50 percent of current cyclic antidepressant use, doxepin for 24 percent, trazodone for 9 percent, imipramine for 6 percent, and other drugs for 11 percent.

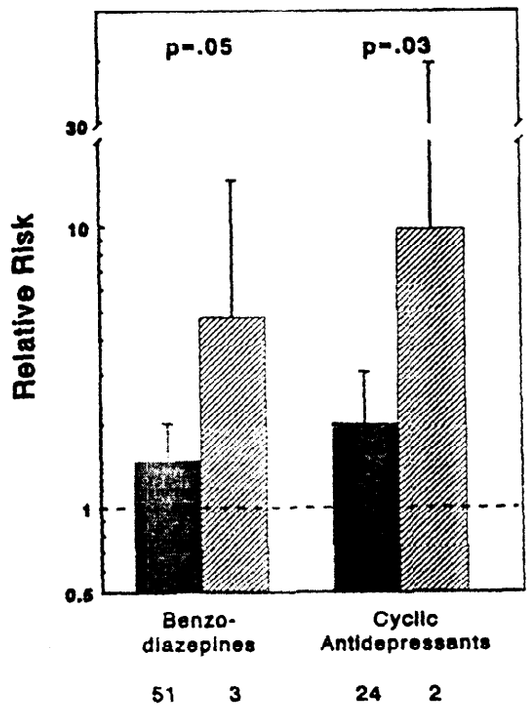

FIGURE 3. Relative risk of involvement in injurious crashes for current users of cyclic antidepressants and benzodiazepines, by number of different drugs received. ■, one drug; ▨, more than one drug. Numbers below columns, number of cases; vertical bars, upper half of the 95% confidence interval. Tennessee Medicaid Crash Study, 1984–1988.

The increased risk of injurious crash involvement among current users of cyclic antidepressants or benzodiazepines was present in subgroups of the cohort defined by sex, race, county of residence, age, and calendar year. The risk was increased for various types of crashes (table 4). There were nonsignificant trends of increased risk for crashes that occurred in the morning, involved speeds ≥45 mph, or involved only a single vehicle. For cohort drivers involved in an injurious crash, the proportion with reported alcohol use was 4.6 percent for both current users and nonusers of psychoactive drugs.

To assess whether other driver characteristics that may be associated with crash risk and psychoactive drug use were confounders, we performed a case-crossover analysis. The estimates of relative risk of involvement in injurious crashes from this analysis were 2.2 (95 percent CI 1.0–4.9) for current use of any psychoactive drug, 1.8 (95 percent CI 1.2–2.9) for indeterminate use, and 0.8 (95 percent CI 0.5–1.1) for former use, which were similar to those from the primary analysis.

DISCUSSION

In the study cohort of 16,262 elderly driver's license holders, 14 percent of the 38,701 person-years of follow-up consisted of pe-

TABLE 4. Relative risk of involvement in injurious crashes for current users of benzodiazepines and cyclic antidepressants, by characteristics of the crash: Tennessee Medicaid crash study, 1984–1988

	Only benzodiazepine		Only cyclic antidepressant		Both		Either	
	Relative risk	95% CI*	Relative risk	95% CI	Relative risk	95% CI	Relative risk	95% CI
Time of day								
6 a.m.–12 p.m.	2.0	1.3–3.2	2.1	1.0–4.6	2.7	1.0–7.3	2.1	1.4–3.1
1 p.m.–7 p.m.	1.1	0.7–1.8	2.2	1.2–4.3	2.0	0.7–5.4	1.4	1.0–2.1
8 p.m.–5 a.m.	1.4	0.4–4.7	1.7	0.2–12.7		—†	1.3	0.4–3.9
Speed ≥ 45 mph‡								
No	1.3	0.9–2.0	1.8	0.9–3.5	1.3	0.9–2.0	1.4	1.0–2.0
Yes	1.7	1.1–2.8	2.7	1.4–5.5	3.3	1.3–8.1	2.0	1.4–3.0
Involved single vehicle								
No	1.4	1.0–2.0	1.9	1.1–3.2	2.1	1.0–4.4	1.6	1.2–2.1
Yes	2.0	0.9–4.7	4.3	1.5–12.5	2.4	0.3–17.6	2.5	1.3–5.0
Property damage > $500								
No	1.3	0.6–2.8	2.2	0.8–6.0	2.4	0.6–9.4	1.5	0.9–2.8
Yes	1.5	1.1–2.2	2.1	1.2–3.7	2.0	0.9–4.6	1.7	1.3–2.3

* CI, confidence interval.
† No current drug users in this subgroup were involved in crashes.
‡ Metric conversion: 72 km/hour.

riods of current psychoactive drug use. This exposure was associated with a 50 percent increased rate of involvement in injurious motor vehicle crashes. The increased risk was confined to current use of benzodiazepines (relative risk = 1.5) and cyclic antidepressants (relative risk = 2.2), where there was a pronounced increase in risk with increasing dose of drug. If this association is causal, then our data suggest that, of the 217,000 injurious crashes that occur each year among elderly drivers (1), at least 16,000 are attributable to psychoactive drug use.

When cohort members were grouped by age, sex, race, residence, and indirect measures of health status, the increased risk of crash involvement among users of psychoactive drugs was present within all subgroups, and there was no statistical evidence that the magnitude of the effect differed between subgroups. Similarly, psychoactive drug use increased the risk for all types of crashes, and the risks for users of individual benzodiazepines and cyclic antidepressants did not differ. The consistency of this effect across demographic and health status subgroups suggests that the study findings may be generalizable beyond the population of Medicaid enrollees, who comprise a small proportion of all elderly drivers. However, other factors such as income that are associated with Medicaid enrollment (44) were not studied. Furthermore, even though our study encompassed nearly 500 crashes, the power to detect differences in subgroup analyses was limited. Additional studies in other populations and of how risk is affected by specific subject, crash, and drug characteristics are needed.

Drug use in the cohort was ascertained from computerized records of prescriptions filled at the pharmacy. These data provided sufficient detail to classify each person-day of follow-up with respect to drug exposure and were not subject to the intentional or unintentional underreporting that is a major problem when self-reports of psychoactive drug use are obtained from persons involved in crashes (30). However, noncompliance or use of drugs from other sources would reduce the accuracy of this measure of drug exposure. Because the resulting misclassification would most probably be nondifferential, it would introduce a conservative bias (45), causing our estimates to underestimate the true risk associated with psychoactive drug use. Thus, exposure misclassification is unlikely to explain the increased crash risk among current users of cyclic antidepres-

sants and benzodiazepines. However, our finding of no significantly increased risk for sedating antihistamines should be interpreted cautiously, as these drugs are widely available in over-the-counter products.

We did not have information on whether persons avoided driving after taking drugs, as is usually recommended for sedating medications. Because the individual benzodiazepines and cyclic antidepressants that accounted for most of the use of these drugs had elimination half-lives ranging from 14 hours (lorazepam (46)) to more than 72 hours (diazepam (47)), regular users could not avoid exposure to psychomotor effects. However, refraining from driving while medicated may partially explain the lack of increased risk for opioid analgesics and antihistamines, where the compounds used most commonly by cohort members had half-lives of 3–8 hours (37).

Two thirds of benzodiazepine use in this population were of drugs such as diazepam, chlordiazepoxide, and clorazepate that have prolonged elimination and persistent psychomotor effects in elderly patients (14, 47). Although the metabolism of lorazepam, which accounted for nearly all of the remaining benzodiazepine use, is little affected by aging, its half-life is 14 hours (46) and, thus, it may have residual sedative effects. Because of concerns with the safety of ultrashort half-life agents such as triazolam (48), the use of these long and intermediate half-life benzodiazepines may increase in elderly patients. It will be important to consider their potential effects on the risk of crash involvement and of other injuries (49).

Amitriptyline and doxepin were the most commonly prescribed cyclic antidepressants, which is consistent with national use patterns in the elderly (33). Among drugs in this class, these tertiary amine compounds have a relatively high incidence of sedative and anticholinergic effects (50) and have been shown to impair road-tracking ability during highway driving (27). Secondary amine compounds such as nortriptyline and desipramine currently are the preferred cyclic antidepressants for elderly patients (50). As the use of these drugs and of specific serotonin reuptake inhibitors with few sedative effects (51) increases in older drivers, further studies to evaluate their effects on driving safety are needed.

There were several potential confounders that were not controlled for directly in the primary analysis, including health status, alcohol use, driving frequency, and drug indication. Poor health could be associated with psychoactive drug use and predispose drivers to either increased risk of involvement in crashes or increased likelihood of sustaining an injury during a crash. However, control for surrogate measures of poor health in the multivariate analysis, including recent history of hospitalization or emergency room visits and use of prescribed medications, did not alter our findings. The lack of an association between former use of psychoactive drugs and crash involvement was further evidence that the association with current drug use did not result from confounding by chronic illness.

Alcohol use is a major risk factor for crashes in younger drivers (52). If our findings were due to confounding by alcohol use, then alcohol use among cohort drivers involved in injurious crashes would have been highest for those who were current users of psychoactive drugs (34). Our data that alcohol use was reported for 4.6 percent of crash involvements among both current users and nonusers of psychoactive drugs indicate that this factor was not a confounder. It is possible that alcohol was an effect modifier that potentiated or enhanced the effects of benzodiazepines and antidepressants (10). However, the very low proportion of crashes with reported alcohol use, which is consistent with behavioral risk factor surveys indicating that fewer than 4 percent of elderly drive after using alcohol (53), suggests that synergistic effects were of limited import.

We did not have information on how frequently cohort members drove. This would be a confounder only if current users of psychoactive drugs drove more frequently than other persons in the cohort. Evidence that such confounding did not occur is provided by the lack of increased risk among former users and by the similarity of results obtained from the case-crossover analysis,

which controls for confounding by subject characteristics that do not change during periods of drug use (42).

There is some evidence that the psychiatric disorders leading to the use of these drugs, particularly depression and dementia, may themselves increase the risk of crash involvement. Major depression is often associated with psychomotor retardation, including impaired information processing, learning, memory, and tracking skills (54). Dementia, in which concomitant depressive symptoms or agitation may lead to prescription of an antidepressant or a benzodiazepine, is associated with marked performance impairment and increased risk of crash involvement (55).

Because we did not have information on affect or cognition, we could not assess the extent to which confounding by indication contributed to the increased crash risk among users of cyclic antidepressants and benzodiazepines. There are two lines of indirect evidence that such confounding does not explain our findings. First, there are data suggesting that, among persons with psychiatric illnesses, drug use independently impairs performance. This has been reported in short-term placebo-controlled trials in persons with major depression (56), high levels of anxiety (57), or periodic insomnia (25). A recent observational study of drivers with dementia found that sedative drug use independently increased the risk of crash involvement (58). Second, the concordance of increased crash risk with periods of active drug treatment and higher doses is most consistent with a drug effect. However, further research to delineate the respective contributions of drug and disease should have high priority because current use of cyclic antidepressants or benzodiazepines, whether because of psychiatric illness or direct drug effects, identified elderly drivers with materially increased risk of crash involvement.

REFERENCES

1. Cerrelli E. Older drivers: the age factor in traffic safety. Washington, DC: US Department of Transportation, 1989. (DOT-HS-807402).
2. Colsher PL, Wallace RB. Longitudinal application of cognitive function measures in a defined population of community-dwelling elders. Ann Epidemiol 1991;1:215–30.
3. Reuben DB, Silliman RA, Traines M. The aging driver: medicine, policy, and ethics. J Am Geriatr Soc 1988;36:1135–42.
4. Williams AF, Carsten O. Driver age and crash involvement. Am J Public Health 1989;79:326–7.
5. Wallace RB, Retchin SM. A geriatric and gerontologic perspective on the effects of medical conditions on older drivers. Hum Factors 1992;34:17–24.
6. Waller JA. Health status and motor vehicle crashes. N Engl J Med 1991;324:54–5.
7. United States Department of Transportation, National Highway Traffic Safety Administration. Conference on research and development needed to improve safety and mobility of older drivers. Washington, DC: US Department of Transportation, 1990. (DOT-HS-807554).
8. Cowart V, Kandela P. Prescription drugs and driving performance. JAMA 1985;254:15–27.
9. Polen MR, Friedman GD. Automobile injury—selected risk factors and prevention in the health care setting. JAMA 1988;259:77–80.
10. Seppala T, Linnoila M, Mattila MJ. Drugs, alcohol, and driving. Drugs 1979;17:389–408.
11. Reidenberg MM, Levy M, Warner H, et al. Relationship between diazepam dose, plasma level, age, and central nervous system depression. Clin Pharmacol Ther 1978;23:371–4.
12. Pomara N, Stanley B, Block R, et al. Increased sensitivity of the elderly to the central depressant effects of diazepam. J Clin Psychiatry 1985;45:185–7.
13. Boston Collaborative Drug Surveillance Program. Clinical depression of the central nervous system due to diazepam and chlordiazepoxide in relation to cigarette smoking and age. N Engl J Med 1973;288:277–80.
14. Greenblatt DJ, Allen MD, Shader RI. Toxicity of high-dose flurazepam in the elderly. Clin Pharmacol Ther 1977;21:355–61.
15. Castleden CM, George CF, Marcer D, et al. Increased sensitivity to nitrazepam in old age. BMJ 1977;1:10–12.
16. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. J Pharmacol Exp Ther 1987;240:159–66.
17. Hindmarch I. The effects of psychoactive drugs on car handling and related psychomotor ability: a review. In: O'Hanlon JF, de Gier JJ, eds. Drugs and driving. Philadelphia: Taylor and Francis, 1986:71–82.
18. Palva ES, Linnoila M, Routledge P, et al. Actions and interactions of diazepam and alcohol on psychomotor skills in young and middle-aged subjects. Acta Pharmacol Toxicol 1982;50:363–9.
19. Seppala T, Mattila MJ, Palva ES, et al. Combined effects of anxiolytics and alcohol on psychomotor performance in young and middle-aged subjects. In: O'Hanlon JF, de Gier JJ, eds. Drugs and driving. Philadelphia: Taylor and Francis, 1986:179–90.
20. Moskowitz H, Smiley A. Effects of chronically administered buspirone and diazepam on driving-related skills performance. J Clin Psychiatry 1982;43:45–55.
21. Bond AJ, Lader pam and buspir logical tests, an 1981;16:212–2(
22. de Gier JJ, 't H. motor perform of outpatients r cology 1981;73
23. O'Hanlon JF, pam impairs l driving. Scienc
24. Betts TA, Birtl actual driving 1982;285:852.
25. O'Hanlon JF, driving perfor 74(suppl 332):
26. Volkerts ER, effects on driv de Gier JJ, ec Taylor and Fr
27. Louwerens JW eral antidepre ing performar In: O'Hanlon ing. Philadel 203–13.
28. Gengo F, Ga namics of d and changes macol Ther
29. Skegg DCG, quilizers and
30. Honkanen R drugs in traf
31. MacPherson reported dru alyzed drive
32. Jick H, Hun and automc tion. Am J
33. Ray WA, Gr and the saf 1992;34:33–
34. Ray WA, C pharmacoe 129:837–49
35. Lessler JT, for postma search Tria tute. 1984.
36. Ruther M, Program s book. 198 Health an cation no.
37. American 6th ed. Ph
38. McCullagh models. 2 1989:193–
39. Payne CD elling ma Oxford, E

43:45–55.
23. Bond AJ, Lader MH. Comparative effects of diazepam and buspirone on subjective feelings, psychological tests, and the EEG. Int Pharmacopsychiatry 1981;16:212–20.
24. de Gier JJ, 't Hart BJ, Nelemans FA, et al. Psychomotor performance and real driving performance of outpatients receiving diazepam. Psychopharmacology 1981;73:340–4.
25. O'Hanlon JF, Haak TW, Blaaw GJ, et al. Diazepam impairs lateral position control in highway driving. Science 1982;217:79–81.
26. Betts TA, Birtle J. Effect of two hypnotic drugs on actual driving performance the next morning. BMJ 1982;285:852.
27. O'Hanlon JF, Volkerts ER. Hypnotics and actual driving performance. Acta Psychiatr Scand 1986; 74(suppl 332):95–104.
28. Volkerts ER, O'Hanlon JF. Hypnotics' residual effects on driving performance. In: O'Hanlon JF, de Gier JJ, eds. Drugs and driving. Philadelphia: Taylor and Francis, 1986:123–36.
29. Louwerens JW, Brookhuis KA, O'Hanlon JF. Several antidepressants' acute effects upon actual driving performance and subjective mental activation. In: O'Hanlon JF, de Gier JJ, eds. Drugs and driving. Philadelphia: Taylor and Francis, 1986: 203–13.
30. Gengo F, Gabos C, Miller JK. The pharmacodynamics of diphenhydramine-induced drowsiness and changes in mental performance. Clin Pharmacol Ther 1989;45:15–21.
31. Skegg DCG, Richards SM, Doll R. Minor tranquilizers and road accidents. BMJ 1979;1:917–19.
32. Honkanen R, Ertama L, Linnoila M, et al. Role of drugs in traffic accidents. BMJ 1980;281:1309–12.
33. MacPherson RD, Perl J, Starmer GA, et al. Self-reported drug usage and crash incidence in breath-alyzed drivers. Accid Anal Prev 1984;16:139–48.
34. Jick H, Hunter JR, Dinan BJ, et al. Sedating drugs and automobile accidents leading to hospitalization. Am J Public Health 1981;71:1399–400.
35. Ray WA, Gurwitz J, Decker MD, et al. Medications and the safety of the older driver. Hum Factors 1992;34:33–7.
36. Ray WA, Griffin MR. Use of Medicaid data for pharmacoepidemiology. Am J Epidemiol 1989; 129:837–49.
37. Lessler JT, Harris BSH. Medicaid data as a source for postmarketing surveillance information. Research Triangle Park, NC: Research Triangle Institute, 1984.
38. Ruther M, Pagan-Berlucchi A, Rinkle V, et al. Program statistics: Medicare and Medicaid data book, 1984. Baltimore, MD: US Department of Health and Human Services, 1987. (HCFA publication no. 03247).
39. American Medical Association. Drug evaluations. 6th ed. Philadelphia: WB Saunders, 1986:81–110.
40. McCullagh P, Nelder JA. Generalized linear models. 2nd ed. New York: Chapman and Hall, 1989:193–208.
41. Payne CD, ed. Generalized linear interactive modelling manual. The GLIM system. Release 3.77. Oxford, England: Royal Statistical Society, 1986.
42. Wilcosky TC, Chambless LE. A comparison of direct adjustment and regression adjustment of epidemiologic measures. J Chronic Dis 1985;38: 849–56.
43. Snedecor GW, Cochran WG. Statistical methods. 7th ed. Ames, IA: Iowa State University Press, 1980:404–7.
44. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol 1991;133:144–53.
45. Rothman KJ. Modern epidemiology. Boston: Little, Brown and Co, 1986:196–213.
46. Bright RA, Avorn J, Everitt DE. Medicaid data as a resource for epidemiologic studies: strengths and limitations. J Clin Epidemiol 1989;42:937–45.
47. Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic research: principles and quantitative methods. Belmont, CA: Lifetime Learning Publications, 1982:220–41.
48. Gilman AG, Goodman LS, Rall TW, et al. The pharmacologic basis of therapeutics. 7th ed. New York: Macmillan, 1985:1694.
49. Salzman C. Pharmacokinetics of psychotropic drugs and the aging process. In: Salzman C, ed. Clinical geriatric psychopharmacology. New York: McGraw-Hill, 1984:32–45.
50. Bixler EO, Kales A, Manfredi RL, et al. Next-day memory impairment with triazolam use. Lancet 1991;337:827–31.
51. Ray WA, Griffin MR, Downey W. Benzodiazepines of long and short elimination half-life and the risk of hip fracture. JAMA 1989;262:3303–7.
52. Salzman C, van der Kolk B. Treatment of depression. In: Salzman C, ed. Clinical geriatric psychopharmacology. New York: McGraw-Hill, 1984: 77–115.
53. Blackwell B. Newer antidepressant drugs. In: Meltzer HY, ed. Psychopharmacology: the third generation of progress. New York: Raven Press, 1987:1041–9.
54. Zylman R. Accidents, alcohol, and single-cause explanations. Lessons from the Grand Rapids Study. Q J Stud Alcohol 1968;(suppl 4):212–33.
55. Stephens T, Schoenborn CA. Adult health practices in the United States and Canada. Comparative and international vital and health statistics reports. Series 5, no. 3. Hyattsville, MD: National Center for Health Statistics, 1988. (DHHS publication no. PHS 88-1479).
56. Linnoila M. Antidepressants and driving. Accid Anal Prev 1985;17:297–301.
57. Kaszniak AW, Keyl PM, Albert MS. Dementia and the older driver. Hum Factors 1991;33:527–37.
58. Linnoila M, Seppala T, Mattila MJ, et al. Clomipramine and doxepin in depressive neurosis. Plasma levels and therapeutic response. Arch Gen Psychiatry 1980;37:1295–9.
59. Linnoila M, Erwin CW, Brendle A, et al. Psychomotor effects of diazepam in anxious patients and healthy volunteers. J Clin Psychopharmacol 1983; 3:88–96.
60. Gilley DW, Wilson RS, Bennett DA, et al. Cessation of driving and unsafe motor vehicle operation by dementia patients. Arch Intern Med 1991;151: 941–6.